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EDITORIAL COMMENT: PITT-ROGERS-DANKS SYNDROME AND WOLF-HIRSCHHORN SYNDROME

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The clinical delineation of multiple malformation syndromes is an interesting process beginning with the recognition of a pattern of anomalies by a clinician. Following the initial report, others follow, often widening the phenotypic spectrum. Sometimes the same syndrome "emerges" with different names in more than one specialist literature. Examples of recently described syndromes include Kabuki, ATR-X and Ohdo blepharophimosis syndromes. Once a pattern has been described the "gestalt" becomes familiar to those with a particular aptitude in syndrome recognition and we all wonder why we didn't recognise the entity before! Studies can then begin on the pathogenesis, and for many syndromes laboratory confirmatory tests eventually are possible. Several recurrent pattern syndromes have been shown to be due to chromosomal microdeletions, for example, Williams syndrome (7q11.23) and Di George syndrome (22q11.2). These microdeletions are not usually visible with routine analysis and clinical suspicion must precede appropriate tests.

If a "new" syndrome is described with very few follow-up reports then caution should be exercised. Pitt, Rogers and Danks [1984] described 4 patients, including 2 sibs, with pre- and post- natal growth retardation and a characteristic face with mid-face hypoplasia. Three further reports were published [Donnai, 1986; Oorthuys and Bleeker-Wagemakers,1989;Lizcano et al., 1995]. In 1991 I was asked to see a child (EK Fig.1 and 2) diagnosed by a colleague as having Pitt-Rogers-Danks syndrome (PRDS).

Fig 1.EK at10 years. Note prominent eyes and triangular face.

Fig 2. EK at 10 years. Note flat malar region.

I noted the similarity of EK to cases A and B in the original report [Pitt et al., 1984] but she also bore similarity to a teenager I had seen with Wolf-Hirschhorn syndrome. Fluorescent *in situ* hybridisation (FISH) studies using Oncor Wolf-Hirschhorn cosmid probe (D4Z1) confirmed that EK was deleted at 4p16.3. Using the same probes, the patient from my previous report [Donnai, 1986] was investigated but no deletion found. I notified one of the authors (JR), of the original report [Pitt et al., 1984] of my

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findings and suggested reinvestigation of their patients. When asked to review a report from Holland of patients with PRDS, again I suggested further investigations looking for deletions of 4p. In this issue, Lindeman-Kusse et al. and Clemens et al. report on 4 patients with PRDS and 4p deletions. Clemens et al. also report reinvestigation of the 2 sibs from the original report [Pitt et al., 1984] which shows that they too have a deletion of 4p16.3 due to a paternal translocation 46,XY,t(4;8)(p16.3;p23.1).

These reports and observations are interesting and important. PRDS was suspected of being an autosomal recessive trait since sibs were affected, but the new cytogenetic findings indicate otherwise. Several reports [McKeown et al., 1987; Altherr et al., 1991; Goodship et al., 1992] show that Wolf-Hirschhorn syndrome (WHS) can result from subtle parental translocations, and that the risk to offspring may therefore extend beyond the nuclear family of the index-case. Are PRDS and WHS the same syndrome or do they result from overlapping microdeletions with differing critical regions? Lindeman-Kusse et al. and Clemens et al. discuss and tabulate similarities and differences of published patients with WHS and PRDS. However, the similarities are compelling, particularly the marked pre- and post- natal growth retardation, microcephaly and the facial gestalt, the latter consisting of prominent glabella, maxillary hypoplasia leading to prominent appearing eyes, low columella, short upper lip and downturned corners of the mouth.

Using DNA probes derived from 4p16.3 the smallest region of deletion overlap in WHS was shown by Gandelman et al. [1992] to be about 2.2 Mb spanning loci D4S166 to D4S90. Tommerup et al. [1993] proposed a zinc-finger gene ZF141 within this region as a candidate for WHS. More recently, Wright et al. [1995] presented an abstract narrowing the WHS critical region further to in the order of 1 Mb ending proximal to D4S96. Zackai et al. [1994] reported on a patient with clinical WHS who was not deleted with the commercially available probe D4F26. The patient was not deleted for cosmids representing the loci D4S95 and D4S93 which are proximal to D4F26; however, cosmids for the loci D4S98 and FGFR3 which are about 300 Kb distal to D4S43 were deleted. A phenotypic map of chromosome region 4p16 was proposed by Estabrooks et al. [1995] confirming that the major facial changes could be attributed to deletion of the critical region defined by Gandelman et al. [1992] and further defined by Zackai et al. [1994].

For the moment the answer to the question "Is PRDS the same disorder as WHS?" cannot be answered with certainty for all cases. Some cases of PRDS are indeed phenotypically and cytogenetically identical to WHS and should be reclassified as such. All remaining cases of PRDS need re-evaluation and reinvestigation using molecular techniques. Those that do not have a 4p deletion should be compared to see if they resemble each other sufficiently for a Pitt-Rogers-Danks syndrome to remain. Perhaps if a WHS gene is identified a mutation should be sought in these patients with non-deletion PRDS. However, for the moment, I will return my first case of PRDS without the deletion [Donnai, 1986] to the "unknown and unclassified" drawer of my filing cabinet.

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